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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/622,492 | 07/21/2003 | Karen Jackson | 330499.00009 | 4987 |

27160 7590 08/08/2006

PATENT ADMINISTRATOR
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EXAMINER

ANDERSON, JAMES D

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1614

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|--------------------------------------|---------------------------------------|--|
| Office Action Summary | Application No. 10/622,492 | Applicant(s) JACKSON, KAREN | |
| | Examiner James D. Anderson | Art Unit 1614 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5,6 and 8-43 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,6 and 8-43 is/are rejected.
- 7) ☒ Claim(s) 42 and 43 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 30, 2006 has been entered.

Status of the Claims

Claims 1-2, 5-6 and 8-43 are currently pending and are the subject of this Office Action. Claims 1, 2, 5 and 8-13 are presently amended.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the United Kingdom on 4/09/2003. It is noted, however, that applicant has not filed a certified copy of the 0208129.7 application as required by 35 U.S.C. 119(b).

Claim Objections

Claims 42 and 43 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Art Unit: 1614

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

In the instant case, claim 42 depends from claim 1, which recites the administration of "devazepide". Claim 42 recites the limitation "wherein the devazepide is substantially the S enantiomer". The specification states that devazepide is 3S-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (page 2, lines 4-6). Thus, it is not apparent how claims 42 and 43 limit claim 1 because devazepide is, by definition, predominately the S enantiomer. The REGISTRY file for devazepide is provided with this Office Action demonstrating that the agent is predominately the S enantiomer.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, 24 and 39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites the limitation wherein the amount of opioid required by the patient is reduced by an amount of "from about 25% to about 75%" in lines 2-3. The limitation is indefinite because the metes and bounds of the amount cannot be readily determined. "From" implies a definite lower limit (in this case, 25%). However, "from

Art Unit: 1614

about” removes this limitation of 25% and renders the claimed amount indefinite because it is not clear to what extent the range has been extended by the word “about”.

Claim 6 is indefinite because it is not apparent exactly which opioids “need to be administered at relatively high or increasing doses”. The skilled artisan must be able to visualize or recognize the metes and bounds of the claimed subject matter. In this case, the claim is limiting independent claim 1 to only opioids wherein the dose is required to be “relatively high” or “increasing”. Exactly what opioids fall into this requirement is not clear.

Claim 6 also recites the limitation “relatively high” in line 2. The claim is indefinite because it is not clear what applicants consider a “relatively high” dose (*i.e.* is 100 mg/kg/day “relatively high”?). In addition, it is not clear what the “relatively high” dose is being compared to (*i.e.* relative to what).

Claim 24 recites the limitation wherein the opioid is administered orally and the devazepide is administered orally. However, claim 24 depends from claim 17, which requires that either devazepide or the opioid be administered intravenously. The method of claim 24 cannot require oral administration of both agents because the claim from which it depends requires that at least one agent be administered intravenously.

Claim 39 recites a fill weight of 150 mg \pm 5% by weight or 300 mg \pm 5% by weight. It is not clear from the claim what the fill weight is based on (e.g. devazepide or other excipients).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2, 5-6, 8-9, 12-24, 27-32 and 36-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/18967 (prior art of record), hereinafter "WO", in view of Dourish *et al.* (prior art of record).

The instant claims are drawn to a method of reducing the amount of an opioid (from 25 to 95%) administered to a patient comprising administering an opioid and a potentiating amount of devazepide. In order to establish a *prima facie* case of obviousness, the prior art must provide the skilled artisan with the motivation to reduce the amount of opioid when it is administered with devazepide.

WO discloses pharmaceutical formulations for treating chronic and neuropathic pain comprising an opioid-potentiating amount of a CCK antagonist and an analgesic amount (*i.e.* a therapeutically effective amount) of an opioid (Abstract). The reference provides the skilled artisan with the motivation to administer a CCK antagonist and an opioid together as well as the motivation to reduce the amount of opioid administered to a patient. The authors disclose that (emphasis added):

"CCK also appears to play a role in the development of tolerance to opioid analgesia as blockade of CCK receptors has been shown to prevent tolerance to morphine. Hence, blockade of CCK

Art Unit: 1614

receptors by CCK antagonists may reverse or prevent the development of opiate tolerance in patients, and also potentiates the analgesic effects of opioids". WO, page 1, lines 23-27.

There is evidence that exogenous CCK attenuates analgesia induced by morphine or release of endogenous opioids (page 1, lines 18-20). The invention of WO is based on the thesis that "blockage of CCK action may be an effective supplement to morphine (or other opioid) administration in the treatment of chronic pain" (page 1, lines 28-30). The formulations disclosed in the reference also comprise a biphasic carrier (page 2, lines 21-28). The components are preferably present in a ratio of 1:2 to 1:40 (CCK antagonist to opioid) (page 5, lines 11-12). The opiate drug includes the opioids recited in instant claim 8 (page 5, lines 13-20) and the CCK antagonist is preferably devazepide (page 6, lines 5-6). The formulations are preferably solid formulations, including tablets (page 7, lines 11-14). Preferable daily doses of the CCK antagonist are in the range of 0.5 to 300 mg per day (page 7, lines 30-31) and, for devazepide, preferably 1-10 mg/day (5-10 mg/day orally or 1-3 mg/day *i.v.*) (page 8, lines 1-2).¹ Intravenous emulsions, infusions and coated S.R. tablets are disclosed (pages 8-11). The intravenous infusion of Example 2 includes 0.015 g MK-329 (devazepide) in 1000 mL and it is stated, "one litre of emulsion may be administered intravenously over a 24-hour period" (page 9, lines 5-21). This amounts to 0.211 mg/kg/day devazepide through intravenous administration (average human weight of 71 kg), thus meeting the limitations of instant claim 32.

¹ The average human weighs approximately 71 kg. Thus, the ranges disclosed in the WO reference are equivalent to 0.07 to 0.14 mg/kg/day (oral) and 14 to 42 µg/kg/day (*i.v.*).

Dourish discloses that the CCK antagonist devazepide potentiates the amount of opioid administered to rats in the tail withdrawal procedure (Abstract, Fig. 2a, Fig. 4). The Dourish reference also provides the motivation to reduce to the amount of opioid administered wherein the authors conclude that:

“[T]he data suggests that devazepide may have therapeutic utility as an adjuvant to morphine analgesia allowing lower doses of the opiate to be used to relieve pain and reducing the risk of opiate-induced respiratory depression” (Abstract).

Devazepide was administered by *i.p.* injection in doses ranging from 1 to 300 µg/kg (Fig. 2a) as well as by *p.o.* administration in doses of 3 to 30 µg/kg (Fig. 4) thus teaching the limitations of claims 27-30. Figure 1 (page 1160) demonstrates the analgesic effect of morphine in the tail withdrawal latencies in the squirrel monkey tail withdrawal test. It is clear from this figure that a dose of morphine above 0.1 mg/kg is required to induce an analgesic effect. Devazepide, when administered alone, induced no analgesia (Fig. 2a, page 1161). However, morphine analgesia was enhanced by *i.p.* injection of devazepide in the squirrel monkey tail withdrawal test (Fig. 2a and Fig. 4). In these tests, 0.1 mg/kg of morphine was administered after administration of devazepide. The amount of morphine administered (0.1 mg/kg) did not induce analgesia when administered alone (Fig. 1). Thus, it is clear from this data that devazepide allows a reduction in the amount of opioid required to induce analgesia when compared to opioid-induced analgesia in the absence of devazepide.

Given the disclosures of Dourish and WO, the instant claims would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Art Unit: 1614

The motivation to combine the references is found in WO wherein it is disclosed that there is evidence that blockage of CCK action may be an effective supplement to morphine. WO also provides the motivation to reduce the amount of opioid administered to a patient (e.g. patients develop tolerance to opioids). In addition, Dourish demonstrates the potentiating effects of devazepide on morphine-induced analgesia. Pharmaceutical formulations of opioids and devazepide, in the ratios and dosages instantly claimed, were known in the art. It was also known that devazepide potentiates the analgesic effect of morphine. Examiner maintains that Dourish clearly demonstrates this to be the case. Thus, the skilled artisan would be imbued with at least a reasonable expectation that a lower dose of opioid could be administered to a patient in need thereof if the opioid were administered with a potentiating amount of devazepide.

Claims 10-11, 25-26 and 33-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/18967 and Dourish *et al.* as applied to claims 1-2, 5-6, 8-9, 12-24, 27-32 and 36-43 above, and further in view of U.S. Patent No. 6,103,261 (Issued August 15, 2000) and Caplan *et al.* (JAMA, 1989, vol. 261, Abstract).

WO and Dourish disclose as above. The '261 patent is provided as evidence that the instantly claimed dosages of opioid were known in the art. For example, '261 discloses oral dosage forms of an opioid analgesic comprising from 15 to 800 mg morphine (column 4, lines 51-54) or 10 to 400 mg oxycodone (col. 4, lines 55-59) thus teaching the limitations of claims 10 and 33-35.

Art Unit: 1614

The Caplan reference is provided as evidence that transdermal administration of the opioid, fentanyl, was known in the art. The safety and efficacy of transdermal fentanyl citrate for postoperative pain management demonstrated that this administration route is safe and effective for treating pain (Abstract) thus teaching the limitations of claims 11 and 25-26.

Thus, the instantly claimed doses and methods of administering opioids would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed June 30, 2006 have been fully considered but they are not persuasive. Applicants argue, *inter alia*, that the teachings of WO and Dourish do not render the instant methods obvious because the prior art did not appreciate that one could lower the dose of opioid in the presence of devazepide, concurrent with improved analgesia.

The 35 U.S.C. § 103 rejections presented above are predicated on the general knowledge in the art that CCK antagonists, specifically devazepide, potentiate the analgesic effect of opioids, specifically morphine. This was well known at the time the instant invention was made. Applicant's invention is based on the observation that the amount of opioid can be reduced "25 to 95%" in the presence of devazepide, concurrent with improved analgesia. However, as discussed *supra*, to lower the dose of opioid in the presence of devazepide would have been *prima facie* obvious in view of the prior

Art Unit: 1614

art. The WO reference provides the motivation to do so and the Dourish reference imbues the skilled artisan with at least a reasonable expectation of success.

Applicants have also argued that Dourish does not suggest that the amount of opioid can be reduced from 25 to 95% by weight (Response, page 16). Applicants further argue that the amount of morphine used in the tests was a “sub-threshold” amount that did not induce analgesia and thus does not render the instant claims obvious. These arguments have been considered but they too are not persuasive.

Doses of 1 to 300 $\mu\text{g/kg}$ of devazepide had no effect on analgesia. A dose of 0.1 mg/kg (sub-threshold amount) of morphine had no effect on analgesia whereas a dose of 0.3 mg/kg morphine doubled the withdrawal latency in the squirrel monkey tail withdrawal test (from 2 to 4 seconds). When 0.1 mg/kg morphine is administered 10 minutes after 1, 3, 10, 30, 100 and 300 $\mu\text{g/kg}$ devazepide, analgesia was increased by approximately 100% (Fig. 2a) compared with the analgesia induced by 0.1 mg/kg of morphine administered alone (Fig. 1). Clearly, when administered together or separately, devazepide allows the amount of opioid to be reduced and results in equal if not greater analgesia.

A reasonable interpretation of the data presented in Figure 1 indicates that a dose of 0.2 mg/kg morphine results in a tail withdrawal latency of approximately 3 seconds. This same 3-second latency can be achieved with a 50% reduction in morphine (0.1 mg/kg) when administered with 30 $\mu\text{g/kg}$ devazepide (Fig. 2a). Thus, the Dourish reference discloses that when morphine and devazepide are administered

Art Unit: 1614

together, the amount of opioid can be reduced from "25% to about 95%" of the opioid required in the absence of devazepide.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Art Unit: 1614



James D. Anderson
Patent Examiner
AU 1614

July 26, 2006



ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER